## REMARKS

### I. Petition for Extension of Time

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office action mailed August 17, 2005 for one month from November 17, 2005 to December 17, 2005. Authorization is given to charge the extension of time fee of $120.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

### II. Claim Rejections – 35 U.S.C. §112

Claims 1, 3-10, 12-18, 20 and 20-29 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 1 has been amended to recite that the core comprises an optional starter seed. Accordingly, antecedent basis is now provided for that term as recited in dependent claims 12, 14, 15 and 29.

Process claim 20 has been amended to recite that delayed release dosage form of claim 1 is obtained with the claimed process. The expressions "wherein the dosage form has no enteric coating" has been deleted.

Applicants submit that no new matter has been introduced by the claim amendments. Withdrawal of the §112 rejections is requested.

### III. Claim Rejections – 35 U.S.C. §103(a)

#### A. US 6,245,351 to Nara et al. ("Nara") in view of US 5,225,202 to Hodges et al. ("Hodges")

Claims 1, 3, 6-8, 12-18, 20 and 25-29 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges.

The core of the claimed dosage form contains a sufficiently large amount of an alkaline agent, i.e., approximately 10 to 35 % by weight of the core material excluding the weight of an

optional starter seed. The alkaline agent acts to neutralize acidic gastric fluids adsorbed through the semipermeable membrane while the dosage form, ***which is not enteric-coated***, passes through the stomach en route to the small intestine.

Nara discloses a drug-containing core which is not enteric-coated and which optionally includes a lubricant, e.g., talc. On page 5 of the Office Action, the Examiner acknowledges that "Nara does not explicitly teach the amount of alkaline additive present in the core". For this purpose, the Examiner relies on the disclosure by Hodges of an enteric-coated tablet core containing an acid-labile drug and a buffering agent within the range of from about 1 to about 20% by weight. The Examiner concludes, therefore, that it would have been obvious to use an alkaline additive in an amount taught by Hodges to obtain a stabile acid-labile composition "because Nara teaches the desirability to obtain a stabile labile composition" (Office Action at page 6). Applicants respectfully disagree.

Firstly, the secondary reference to Hodges is directed to ***enteric-coated*** pharmaceutical compositions. As such, Hodges does not recognize the problem solved by the claimed invention which is directed to oral dosage forms which are not enteric-coated. Therefore, it is indisputable that Hodges teaches away from both Nara and the claimed invention because the pharmaceutical formulations disclosed by Hodges have an enteric coating which protects the acid-labile active ingredient from the acid gastric fluid during its passage through the stomach. Accordingly, the person of ordinary skill in the art who is interested in formulating a dosage form without an enteric coating layer, wherein the core contains an acid-labile substance, would have had no motivation to consider Hodges alone or in combination with Nara.

Secondly, there is no support for the Examiner's allegation that "Nara teaches the desirability to obtain a stable acid labile composition". While it is true that Nara discloses a broad range of possible active ingredients (col. 3, lines 35-63), including omeprazole and lansoprazole, ***Nara is silent*** with respect to the unique problems associated with the formulation of dosage forms having an acid-labile substance as the active ingredient. This is no surprise since Nara is concerned with opiod compounds which are expressly preferred by Nara (col. 3, line 65).

In support of their position, Applicants rely on the complete absence of any disclosure, suggestion or recognition by Nara of the necessity of including a sufficiently high amount of an

alkalizing agent in a core, which core is not protected by an enteric coating, to neutralize gastric acid fluids adsorbed through the coating composition. Specifically, Nara states that the dosage form may ***optionally*** contain a lubricant, i.e., talc, which is typically present in a formulation at a 5% concentration. Applicants submit that the optional inclusion of a nominal amount of an alkaline agent is hardly an expression of "the desirability to obtain a stable acid-labile composition". Rather, it is evidence of Nara's failure to recognize the unique problems associated with the formulation of solid, oral formulations of acid-labile drugs and the need to protect the acid-labile drugs from the acidic environment of the stomach, especially when the dosage form is not enteric coated.

In conclusion, Applicants submit the following:

- Contrary to the Examiner's allegation, the primary reference to Nara does not teach or even suggest the desirability to obtain a stable acid-labile composition. At best, Nara discloses the optional inclusion of a nominal amount of an alkaline agent in the drug-containing core as a lubricant.
- The secondary reference to Hodges is not analogous to either Nara or the claimed invention because the pharmaceutical formulations disclosed by Hodges have an enteric coating which protects the acid labile active ingredient. The person of ordinary skill in the art who is interested in formulating a dosage form without an enteric coating layer, wherein the core contains an acid-labile substance, would have had no motivation to consider Hodges alone or in combination with Nara.
- Neither Nara nor Hodges, whether taken alone or in combination, provides the requisite motivation or suggestion to formulate a core containing an acid-labile substance and a sufficiently large amount of an alkaline agent, i.e., approximately 10 to 35 % by weight of the core material excluding the weight of an optional starter seed, to neutralize acidic gastric fluids adsorbed through the semipermeable membrane while the dosage form, which is not enteric-coated, passes through the stomach en route to the small intestine.

Accordingly, the Examiner has failed to establish a *prima facie* case obviousness. Withdrawal of the §103 rejection of claims 1, 3, 6-8, 12-18, 20 and 25-29 in view of the combination of Nara and Hodges is requested.

**B. Nara, Hodges and US 5,820,852 to Burgess et al. ("Burgess")**

Claims 8 and 9 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges and Burgess.

At page 6 of the Office Action, the Examiner acknowledges that Nara and Hodges are silent as to the claimed alkaline agent. For this purpose, the Examiner relies on the disclosure by Burgess of buffering agents to adjust the pH of oral compositions to a pH within the range from about 9 to about 10.5. The Examiner concludes that it would have been obvious to combine Burgess with Nara and Hodges, especially in view of the use by Hodges of buffering agents within the range of from about 1 to about 20%.

Applicants respectfully disagree. Firstly, Burgess is directed to oral compositions, e.g., toothpaste. The toothpaste art is nonanalogous to pharmaceutical dosage forms which are prepared to have a specific release rate and target in the gastrointestinal tract to achieve the desired therapeutic purpose. Specifically, Burgess is not at all related to the pharmacological art of formulating an acid-labile substance in an oral dosage form which, after ingestion, must (a) travel through the acidic environment of the stomach, (b) maintain its release profile and (c) arrive at the target site without degradation. As such, the rigors of preparing the claimed invention are unique relative to the toothpaste art. Accordingly, a person of ordinary skill in the art who is interested in formulating a dosage form comprising an acid labile substance such as omeprazole without an enteric coating layer would not turn to the toothpaste art including Burgess.

Secondly, Burgess fails to overcome the deficiencies of Nara and Hodges. For the reasons given in the preceding Section III(A), the primary reference to Nara does not teach or even suggest the desirability to obtain a stable acid labile composition. Furthermore, the secondary reference to Hodges teaches away from both Nara and the claimed invention because the pharmaceutical formulations disclosed by Hodges have an enteric coating which protects the acid labile active ingredient.

In conclusion, Nara , Hodges and Burgess, whether taken alone or in combination, fail to provide the requisite motivation or suggestion to support the obviousness rejection. Accordingly, the Examiner has failed to establish a *prima facie* case obviousness.

Withdrawal of the §103 rejection of claims 8 and 9 is requested.

C. **Nara, Hodges and WO 98/54171 ("Cotton")**

Claims 4, 5 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Hodges and Cotton.

As stated by the Examiner on page 4 of the Office Action, Cotton is cited for the disclosure of the magnesium salt of S-omeprazole as an active ingredient. Applicants submit that Cotton does not over come the deficiencies of Nara and Hodges to suggest the claimed invention for the reasons given in Section III(A). Withdrawal of the §103 rejection of claims 4, 5 and 23-26 is requested.

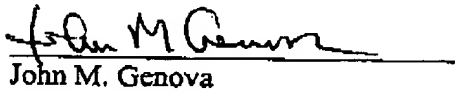
## CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-10, 12-18, 20 and 23-29 are in condition for allowance, which action is earnestly solicited.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 15 December 2005

Respectfully submitted,



John M. Genova
Reg. No. 32,224
Direct Dial: (212) 819-8832

Customer No. 07470
White & Case LLP